UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

PC 129067

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MAR 17 1992

MEMORANDUM

SUBJECT: Difethialone: New Chemical Screen of Toxicology Data Submitted by the Registrant.

Caswell No: 114AAB
HED Project No: 2-1522
MRID Nos: 415785-01; 416733-01 through 416733-05; 420650-06 through 420650-13; 421143-01; 422038-01 through 422038-04.

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THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y M Ioannou 3/12/92
Review Section I, Toxicology Branch II
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and

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Registrant: LiphaTech, Inc., Milwaukee, WI

Action Requested: New Chemical Screening Review of the following Toxicology Data submitted by the registrant for Difethialone:

§ 81-1 Acute Oral Toxicity in Rats
§ 81-2 Acute Dermal Toxicity in Rabbits (5 studies: 3 range-finding, 2 median lethal dose studies)
§ 81-6 Dermal Sensitization in Guinea Pigs
§ 83-3(a) Developmental Toxicity in Rats
§ 83-3(b) Developmental Toxicity in Rabbits
§ 84-2(a) Mutagenicity- Gene Mutation (CHO cells)
§ 84-2(b) Mutagenicity-Structural Chromosome Aberrations (human lymphocytes)
§ 85-1 Metabolism in Rats
§ 86-1 Acute and Subacute Toxicity in Hogs
§ 86-1 Antidotal Treatment Following Overexposure in Rats and Dogs (2 studies)

Recommendation:

The currently submitted studies have been subjected to New Chemical Screening Review. The conclusions of Toxicology Branch II are listed below:

1) Difethialone did not pass the New Chemical Screen based on the fact that the Metabolism Study in Rats did not meet the acceptance criteria.

2) The registrant has submitted mutagenicity studies in support of the Subdivision F guideline requirements for **Gene Mutation** (MRID # 407914-04, previously reviewed and found acceptable; MRID # 420650-08, submitted with this data package) and **Structural Chromosome Aberration** (MRID # 407914-05, previously reviewed and found unacceptable; MRID # 420650-07, submitted with the present data package). However, no studies in support of **Mutagenicity-Other Genotoxic Effects** have been submitted to fulfill this requirement. The registrant is required to submit an acceptable study in support of this data requirement for registration of difethialone.

3) Acute toxicity studies were previously submitted for the technical grade of difethialone. None of these studies were acceptable, with the exception of an Acute Oral Toxicity Study in Dogs (MRID # 414422-01). However, the dog is not an acceptable species for acute toxicity testing. Thus, the registrant is required to submit data which will upgrade the existing acute toxicity studies on the technical grade of difethialone to at least core minimum data, or submit new studies with the technical grade of difethialone conducted in an acceptable species (the rat). In addition, a study on the dermal sensitization of difethialone technical grade was never submitted and is required.

4) The Developmental Toxicity Study in Rabbits submitted with the present data package did not meet the acceptance criteria for formal review. However, based upon the Rat Developmental Toxicity Study, which was found acceptable for review, a new rabbit Developmental Toxicity Study may not be required pending acceptance of the rat study after formal review.

Studies Submitted by LiphaTech, Inc. for Registration of Difethialone

Difethialone Technical:

Developmental toxicity in rabbits, MRID #'s 422038-03; 422038-04

Developmental toxicity in rats, MRID #'s 422038-01; 422038-02

Mutagenicity-Gene Mutations in Chinese Hamster Ovary Cells, MRID # 420650-08

Mutagenicity-Structural Chromosome Aberrations in Human Lymphocytes, MRID # 420650-07

Metabolism in rats, MRID #'s 420650-09; 420650-10

Acute Toxicity in Hogs, MRID # 420650-12

Subacute Toxicity in Hogs, MRID # 420650-12

Antidotal Treatment Following Overexposure in Rats, MRID # 420650-13

Antidotal Treatment Following Overexposure in Dogs, MRID # 421143-11

Difethialone 0.5% Dry Concentrate

Acute Oral toxicity in rats, MRID # 420650-06

Single Dose Dermal Toxicity in Rabbits, MRID #'s 416733-01 through 416733-05

Dermal Sensitization in Guinea Pigs, MRID # 415785-01

SCREENING REVIEW
Difethialone Technical
Difethialone 0.5% Dry Concentrate

Acute Studies Previously Submitted

Acute Toxicity data for Difethialone technical and Difethialone Pellets (0.0025% a.i.) were previously submitted and reviewed by the Agency. For the technical grade of difethialone, all studies were found to be supplementary. In addition, no dermal sensitization study for difethialone technical was found. For difethialone pellets (0.0025% a.i.), all studies were found to be core minimum or guideline, with the exception of the primary eye irritation study, which was graded as supplementary. No acute inhalation study for difethialone pellets was found.

Studies Submitted with the Present Data Package:

Acute studies with difethialone 0.5% dry concentrate:

Acute Oral MRID # 420650-06

Meets acceptance criteria for review.

Acute Dermal MRID #'s 416733-04 and 416733-05

Prior to conduct of these studies, 3 range-finding studies were conducted. Based on the results of the third range-finding study, the dermal toxicity test was conducted. The first test produced excessive mortality at the highest dose used in the third range-finding study. A second dermal toxicity study was conducted at lower doses. This second study meets the acceptance criteria for review.

Dermal Sensitization MRID # 415785-01

Reviewed by Toxicology Branch II (document # 008233). Graded as core guideline.

Developmental Toxicity in Rats

MRID #'s 422038-01 (preliminary study); 422038-02 (main study)

Meets acceptance criteria for review. It was not known whether the study was conducted in accordance with 40 CFR 160.

Developmental Toxicity in Rabbits

MRID #'s 422038-03 (preliminary study); 422038-04 (main study)

Does not meet acceptance criteria for review. A dose high enough to produce significant maternal toxicity was not obtained in either the preliminary or main study. It was not known whether the study was conducted in accordance with 40 CFR 160.

Mutagenicity-Gene Mutation

MRID # 420650-08

Meets acceptance criteria for review.

Mutagenicity-Structural Chromosome Aberration

MRID # 420650-07

Meets acceptance criteria for review.

Metabolism in Rats

MRID #'s 420650-09; 420650-10

Does not meet acceptance criteria for review. Only two rats per sex per time point used for determination of plasma radioactivity after oral dosing. Only one rat per sex per time point used for determination of tissue radioactivity after oral dosing. Only one rat per sex per time point used for determination of excretion of test article derived radioactivity. Dose groups selected received only single oral doses; no repeated oral dose group or intravenous dose group. It was not known whether the study was conducted in accordance with 40 CFR 160.

Domestic Animal Safety

Acute Oral Toxicity in Hogs

MRID # 420650-12

No specific criteria are available to determine the acceptability of this study. It appears from examination of this study that it would be acceptable for review based upon the acceptance criteria for § 81-1 guideline studies. However, the assignment of a toxicity category may not be possible for this study.

Subacute Toxicity in Hogs

MRID # 420650-11

No acceptance criteria exist for this type of study.

Antidotal Treatment Following Overexposure in Rats and Dogs

MRID #'s 420650-13 (rat study); 421143-01 (dog study)

The criteria for acceptance of these studies are those based upon protocols submitted to and reviewed by the Agency from the registrant (July 14, 1989 memorandum from Ray Landolt to Steve Palmateer). Only the dog protocol was found within the memorandum. However, protocols for each study were attached to the studies themselves.

Based upon the available information for the rat and dog protocols, the antidotal treatment studies in rats and dogs appear acceptable for review.

Recommendation:

The submitted studies as listed on page 2 of this memorandum have been subjected to New Chemical Screening Review. Difethialone did not pass the New Chemical Screen for the reasons listed on page 2 and 3 of this memorandum.

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Chemical:	**Difethialone**
PC Code:	**128967**
HED File Code	**13000 Tox Reviews**
Memo Date:	***03/17/1992***
File ID:	**00000000**
Accession Number:	**412-01-0168**

HED Records Reference Center
06/25/2001